Platelet Bleeding

Introduction

Platelet bleeding presents with **superficial bleeding**, microhemorrhages into **mucosal surfaces**. This presents as **gingival hemorrhage**, heavy menses (**menorrhagia**), **hematuria**, and **epistaxis**. Platelets form the platelet plug and are not involved in clotting factors or secondary hemostasis. That means that bleeding caused by platelet problems should show **no change to the PT or PTT**. You should know that the **bleeding time** is a marker for platelet problems, being prolonged in platelet diseases. The bleeding time is performed by cutting the patient's skin, then timing how long it takes to stop bleeding. It is a test that is never performed. It is information that you may receive in a clinical vignette, however. A normal bleeding time means no problems with platelets; a prolonged bleeding time means problems with platelets. **Platelet factor assays** are available, though are not commonly used.

All bleeding can be clinically reasoned into platelet bleeding and factor bleeding. If someone is bleeding in front of you, the appropriate next step is both complete blood count and coagulation panel. When clinically reasoning, you want to start thinking, "*superficial bleeding gets a CBC while deep bleeding gets a coagulation panel*," separating the thought process into primary hemostasis/platelets and secondary hemostasis/factors. In this lesson, we consider platelet problems only.

Platelet problems can be further siloed into problems of **platelet number** (thrombocytopenia) or **platelet function** (thrombocyte dysfunction). While all platelet bleeding results in mucosal hemorrhages, only thrombocytopenia results in cutaneous hemorrhages—petechiae and purpura. You are committed to platelet bleeding on clinical reasoning. You will obtain a CBC. The initial clinical reasoning tree involves recognizing the skin findings and anticipating thrombocytopenia. **Thrombocytopenia** is caused by production (TPO defects or bone marrow suppression), destruction (HIT, TTP, DIC, ITP), or sequestration (cirrhosis). **Platelet function** is inhibited by several pharmacologic agents, uremia, and some rare genetic disorders.

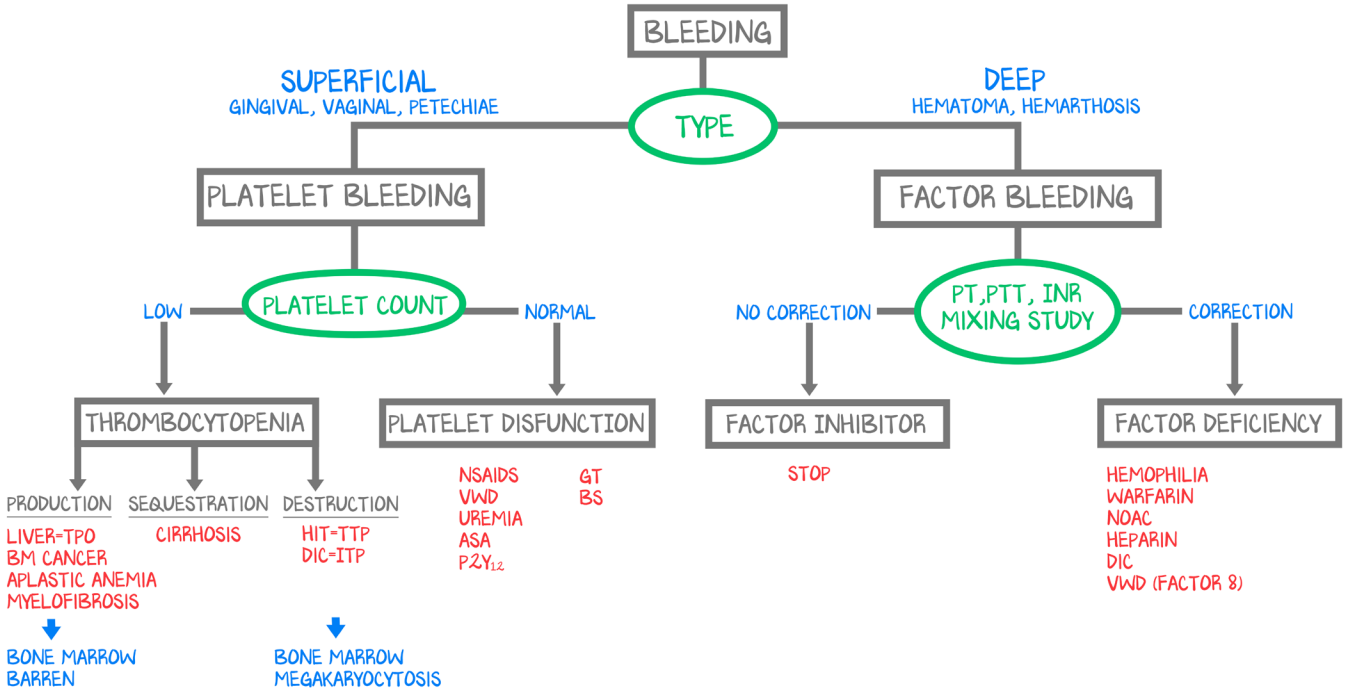

Figure 4.1: Initial Decision Tree on Bleeding

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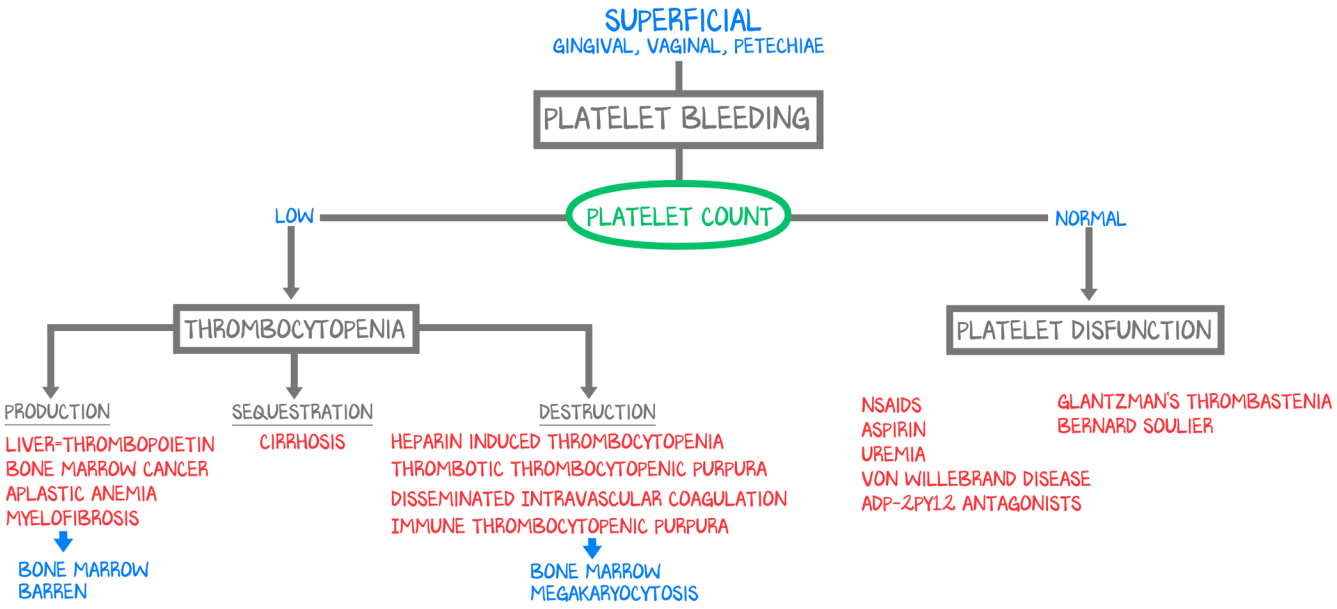

Figure 4.2: Initial Decision Tree on Bleeding and Platelet Bleeding
With the factor bleeding removed, this illustration gives the details without the abbreviations. The first main decision is whether there is a platelet dysfunction (normal platelet count) or platelet deficiency (low platelet count). For deficiency, there are many possible reasons, so are further bucketed into production, destruction, and sequestration.

Even without that dedicated clinical reasoning pathway, obtaining a coagulation panel rules out a disorder of secondary hemostasis, and a CBC informs you whether the platelets are low or not. The results of those two tests inform you that (1) it is platelet bleeding because it isn't factor bleeding (the PT and PTT are normal), and (2) it is platelet function or count (normal count means function; low number means low count).

We discuss in this lesson dysfunctions of platelet function first, then transition to disorders of platelet number—TTP/HUS, DIC, HIT, and ITP.

Dysfunctions of Platelet Function

Platelet adhesion, activation, and aggregation. The formation of the platelet plug. The end of primary hemostasis. These are all things you have seen before. In fact, there is very little to discuss in this lesson that hasn't been discussed in previous lessons. But let's review platelet physiology briefly, superimposed on the pharmacology you already know, and use that to layer on the inheritable diseases that can cause platelet bleeding.

Endothelial trauma leads to the release of Weibel-Palade bodies from the endothelial cell. VWF binds to subendothelial collagen. VWF binds to gly1b of platelets. These platelets are now adhered to the site of injury. They release α-granules containing TXA_2 and ADP, which in turn bind to receptors on platelets passing by that are not adhered to the site of injury. This activates platelets. Platelet activation results in those activated platelets expressing gly2b/3a on the plasma membrane surface. All platelets release more α-granules and dense bodies. Dense bodies contain fibrinogen. Fibrinogen cross-links neighboring platelets via gly2b/3a.

Drugs can cause platelet dysfunction. Most of the drugs that impair platelet function are administered specifically to prevent the formation of arterial clots. Aspirin irreversibly inhibits COX-1 and COX-2, which reduces the amount of TXA_2 produced by platelets and effectively inhibits TXA_2-R. Clopidogrel and other ADP-$P2Y_{12}$ antagonists irreversibly inhibit the ADP-R directly. Abciximab inhibits

glycoprotein 2b/3a. Some drugs have an unintended effect on platelet function—NSAIDs are used as fever reducers and pain relievers, but reversibly bind COX-1 and COX-2, so can lead to bleeding. **Uremia** is another cause of platelet dysfunction.

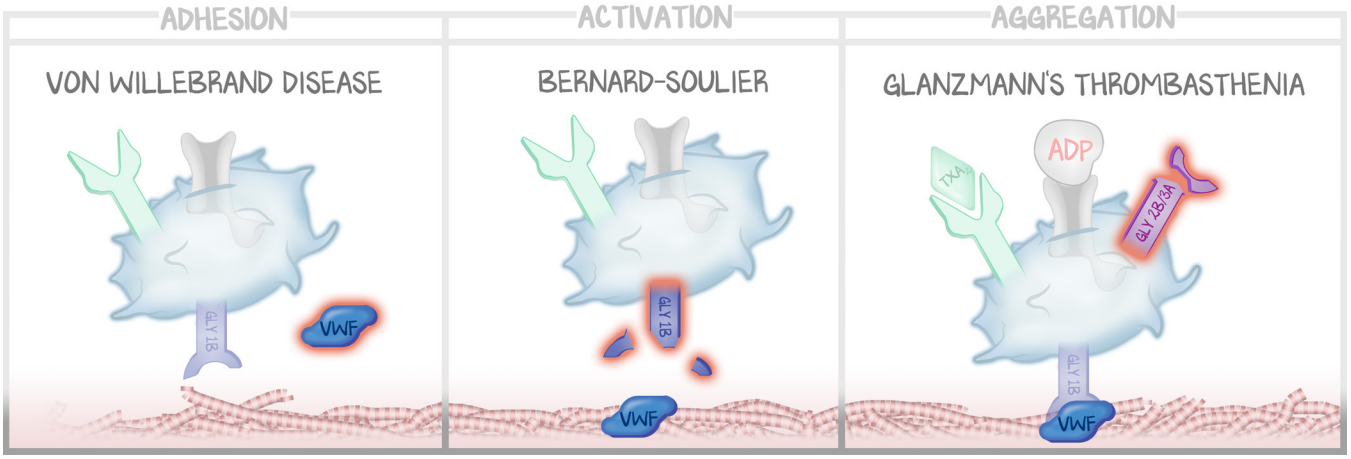

Figure 4.3: Dysfunction of Platelet Function
In von Willebrand disease there is a deficiency of von Willebrand Factor, which compromises platelet adhesion. In Bernard-Soulier there is a deficiency of glycoprotein 1b, compromising platelet activation. In Glanzmann's thrombasthenia, there is a deficiency of glycoprotein 2b/3a, compromising platelet aggregation.

We now apply the information in the previous paragraphs and in Figure 4.3 to discuss inheritable diseases of platelet bleeding.

There are inheritable conditions that affect the glycoproteins involved in the formation of the platelet plug. They are both rare and mild in terms of their symptoms, and have no management tool. They remain the subject of board examinations because there are overlaps in the mechanism of disease and mechanism of drugs. Linking a rare disease to a pharmacologic agent makes for an easy vignette. **Bernard-Soulier** has "one B" in its name, has the B in the first part of the eponym, and alphabetically (compared to Glanzmann's thrombasthenia) comes first. This is the memory cue to remind you that Bernard-Soulier is caused by an impairment in **glycoprotein 1b**. The other inheritable disease of glycoprotein dysfunction is **Glanzmann's thrombasthenia**, which is a deficiency of the **other** glycoprotein, **glycoprotein 2b/3a**.

Von Willebrand disease (VWD) is an inherited deficiency of von Willebrand factor. It is **autosomal dominant,** the **most common** inheritable bleeding disorder, but is usually **quite mild**. VWF is released by endothelial cells at the site of injury and by platelets during activation. The reduced VWF **impairs adhesion**. VWF also stabilizes factor 8. With reduced VWF, there is a relative **factor 8 deficiency**. Because of the factor 8 deficiency (which is a cofactor for the activation of factor 9 in the intrinsic pathway), the **PT may be elevated**. Because of the VWF defect, platelet function is compromised and there will be a **prolonged bleeding time**, but a normal platelet number. The VWF level, measured as the **ristocetin cofactor activity**, is reduced, demonstrating **no agglutination**. Most patients who have the disease are unaware they have it until a major hemostatic stressor (surgery, dental extraction, childbirth) uncovers it. No cause of VWD has zero VWF activity, and so treatment involves **inducing more VWF release** from endothelial cells using **desmopressin**. Since the effect is limited in duration, desmopressin is administered only during periods of hemorrhage.

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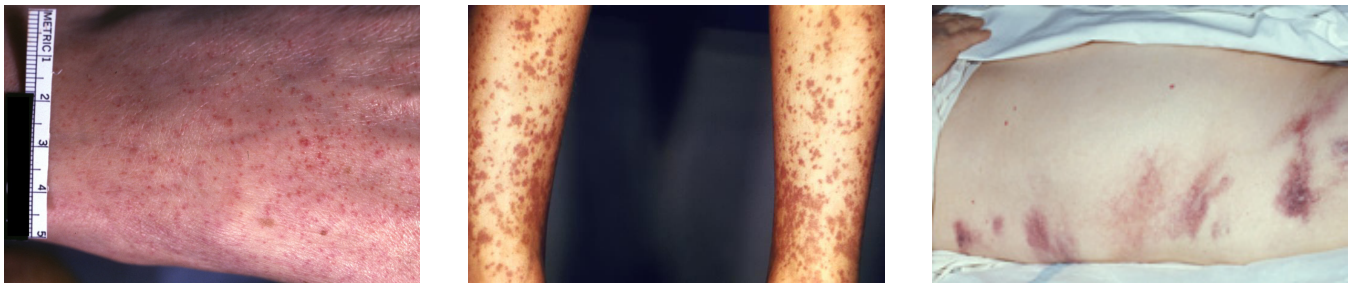
Diseases of Platelet Number

Thrombocytopenia is defined by a platelet count below the normal level, 150,000. Symptoms of thrombocytopenia are usually negative until the platelet count gets below 50,000. Intervention is required only when there is bleeding and a low number (< 20,000) or when the platelet count gets into the single digits. The risk of profound thrombocytopenia is **spontaneous intracerebral hemorrhage**. While patients with low platelets may have a prolonged bleeding time, the absence of platelets does more than prevent the formation of the platelet plug. Platelets also induce the endothelium to remain tight. With thrombocytopenia, the endothelium loosens, the space between endothelial cells becomes large enough for red blood cells to leak out. This forms **petechiae**—pinpoint hemorrhages of the skin (< 3 mm). When these pinpoint hemorrhages begin to coalesce or get larger, they are referred to as **purpura** (> 5 mm). Even larger accumulations of red blood cells in the skin are called **ecchymoses** (> 1 cm). They are all caused by extravasation of red blood cells into the skin. This is bleeding, technically, but is a microhemorrhage and does not represent endothelial injury, only dysfunction. Petechiae is a product of platelet number, and is not seen in medication side effect, VWD, or the inherited conditions discussed above.



(a) (b) (c)

Figure 4.4: Thrombocytopenia Skin Findings
(a) An example of petechiae, pinpoint red dots that do not blanche when pressed. (b) Purpura is a the confluence of those pinpoint dots. (c) Ecchymoses, a bruise.

Platelet number may be reduced by **sequestration** in the spleen (as seen in cirrhosis), by a **production** issue of the marrow (as seen in myelodysplastic syndrome, aplastic anemia, and bone marrow cancers), or by **destruction** of platelets in circulation, the subject of the remainder of the lesson.

You will be tasked with recognizing the syndromes of platelet destruction, which is why the rest of the lesson is committed to those syndromes. But you will also be tasked with understanding the system. That is usually done through TPO levels and a bone marrow biopsy. Rarely does an isolated thrombocytopenia provoke a bone marrow biopsy in clinical practice. But the appearance of the bone marrow in various clinical states—what the bone marrow would look like if one were done—is a common method of testing your knowledge of the syndrome being presented. Levels of thrombopoietin (TPO) are not assessed in clinical practice. But, like the bone marrow biopsy, a licensing exam may give you the TPO level as a means of deducing the answer; or, conversely, you may be asked to anticipate the TPO level given the information at hand to assess your knowledge of the system.

Thrombogenesis occurs in the bone marrow in response to thrombopoietin (TPO). When the platelets fall in the blood, TPO is released from the liver. TPO tells the marrow to make more platelets. The platelet precursor becomes a megakaryoblast, which in turn becomes a **megakaryocyte**, and blobs of plasma membrane and cytoplasm pinch off the megakaryocyte to become a **thrombocyte**, a platelet. When there is a signal to produce more platelets, that signal is interpreted by the marrow to make more megakaryocytes. If the marrow is healthy, the marrow will respond. Megakaryocytes

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increase in number and size. Giant megakaryocytes are a sign of increased platelet synthesis and are reflective of an increased TPO. If there is a proliferative marrow and TPO is low, that is considered a **myeloproliferative disorder** (Proliferation #2: *Myeloproliferative Disorders*). If there is a proliferative marrow and TPO is high, then something is driving that proliferation. That is likely to be a **destruction** thrombocytopenia. If TPO is high, but the marrow is the cause of thrombocytopenia, then the bone marrow biopsy would not reveal proliferation. This is a **production** thrombocytopenia. In its place you might find absent cellularity (aplastic anemia), sclerosis/collagen/fibrosis (myelofibrosis), or fat (yellow marrow is not hematopoietic).

All of the destruction thrombocytopenias that follow will share elevated levels of TPO and megakaryocytes on bone marrow biopsy. Although these laboratory tests are not used to make the diagnosis or evaluate the condition, interpretation of labs on a vignette requires your understanding of thrombocytopenia. The administration of platelets to improve the platelet count isn't always the right move. Pay attention to which condition you definitely should give platelets and which you should definitely not.

Platelet Count—Destruction—Immune Thrombocytopenic Purpura (ITP)

Immune thrombocytopenic purpura presents with **purpura** (and petechiae) because of **thrombocytopenia** caused by an **immune** phenomenon. Autoantibodies form against platelets, marking them for splenic destruction. The antibodies are **IgG** against **glycoprotein 2b/3a**. Just as IgG tags a circulating antigen for phagocytosis, so too does IgG tag the platelet. Splenic macrophages identify the IgG-tagged platelets and phagocytose them, carrying out the normal function of the spleen's red pulp. The spleen's white pulp has an abundance of B cells. The spleen's white pulp may be a source of the IgG antibodies, suggested by the fact that the majority of splenectomies cure ITP. However, because some cases relapse after splenectomy, the true source of the antibodies may be elsewhere. Splenectomy definitely removes the primary site of splenic destruction (the red pulp), but only usually removes the site of antibody generation. If an antibody were produced outside the spleen, and the spleen were removed, the remainder of the reticuloendothelial system (liver, bone marrow) could still destroy tagged platelets.

There are two forms of the disease: the acute form (children) and the chronic form (autoimmune disease, adult women).

In the **acute** form of the disease, often found in **children following viral infections**, there is a self-limiting reduction of platelets that starts 3 weeks after the virus and may last up to 6 months. Most cases need not be treated (only monitored), and resolve spontaneously. Steroids may be used, but often aren't needed. The more aggressive therapies, discussed below, are essentially never needed in the acute form of the disease.

In the **chronic** form of the disease, often found in **women of reproductive age**, there is a relapsing and remitting course. When by itself (without any other syndrome), it is called idiopathic or primary chronic ITP. When caused by another autoimmune disease, it is called secondary chronic ITP. Secondary ITP is often secondary to **autoimmune disease such as lupus** or a malignancy of B cells. B cells produce antibodies. Almost all patients with chronic ITP respond to **corticosteroids** (which inhibit phagocytosis), but almost all eventually relapse. Long-term chronic steroid administration must always be avoided because of the deleterious side effects (osteoporosis, hypertension, diabetes, etc.). During acute flares, where platelet counts get critically low (ITP is the only of these destructive diseases that will present with a single-digit platelet count), **intravenous immunoglobulin** (IVIG) can be given to temporarily hide the platelets from phagocytic destruction. IVIG saturates phagocyte Fc receptor sites so the Fc portions of the antibodies attached to platelets cannot bind to the Fc receptor on macrophages. In ITP, IVIG is equivalent to **plasmapheresis**, in which the patient's blood is passed through a filter

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that removes the antibodies. Both are only temporary solutions, used when steroids fail or when the risk of bleeding is profound. Because the spleen is thought to be both the source of the antibodies and the site of phagocytosis, **splenectomy** is performed in refractory cases. If splenectomy is not possible, or there is recurrence after splenectomy (implying that the antibody may come from any B cell, not just those in the spleen), **rituximab** is used. Rituximab is an anti-CD20 monoclonal antibody that reduces B-cell immunity.

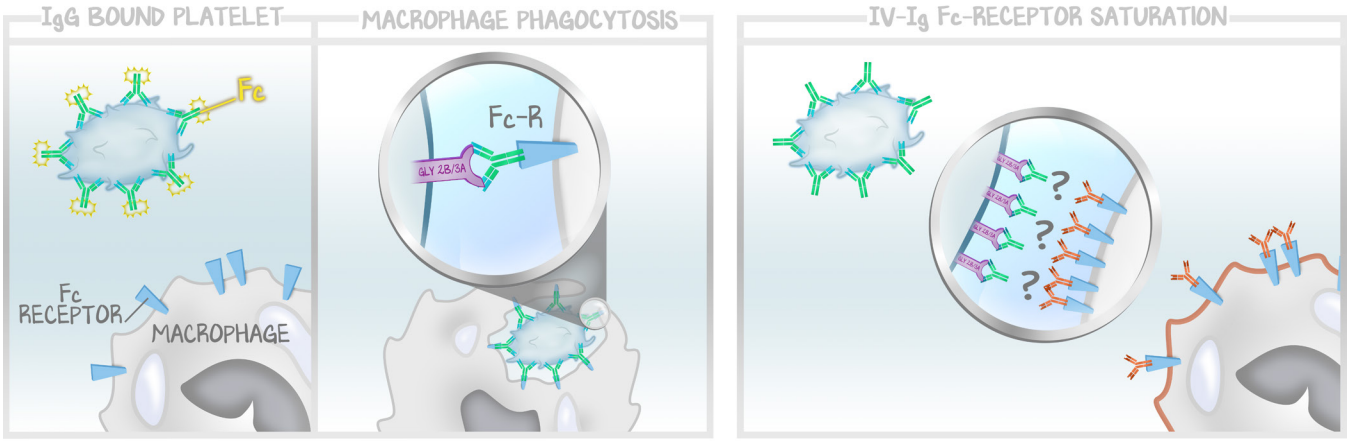

Figure 4.5: ITP Pathogenesis and Treatment
Platelets tagged with antibody are phagocytosed by macrophages because the Fc receptor on macrophages binds to the Fc portion of the antibody while the Fab portions are bound to the platelet. By giving intravenous immunoglobulin, saturation of the macripahge Fc portions means that there are none available to bind to the Fc portion of the antibody bound to the platelet. The antibodies are not removed, but the macrophage destruction of the platelets is prevented.

If ever an ITP patient is bleeding and has a low platelet count, **give platelets** (in contrast to the next disease, which is also antibody mediated).

Thrombotic Thrombocytopenic Purpura (and HUS)

Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) have very different disease courses—HUS is generally benign, self-limiting, seen in children, following bloody diarrhea, while TTP is generally life-threatening, seen in adults, and associated with a genetic deficiency—but have extremely similar presentations at the start. When you first see the patient with schistocytes in their blood and thrombocytopenia, you cannot be sure whether what you have in front of you is HUS—supportive care only—or TTP—plasma exchange to prevent death. So the diseases are taught together as one common disease. Together, they account for the **thrombotic microangiopathies**. For your licensing exam, Figure 4.1 is what you should memorize. For life, learn these two diseases as a spectrum of thrombotic microangiopathies.

TTP presents with **thrombocytopenia**, so causes **purpura** (and petechiae). The thrombocytopenia is caused by the formation of arterial **thrombi**, which consume platelets. This happens in small blood vessels. In small blood vessels, arterioles and capillaries, red blood cells must deform to fit through the vessel. The lumen is already quite narrow. The addition of a thrombus, no matter how small, can lead to shearing forces acting on red blood cells passing by. In TTP, **platelets are consumed** to make miniature platelet thrombi in **small blood vessels**. The platelet thrombi are too small and unassociated with subendothelial collagen to induce the formation of a fibrin clot, so **factor clotting does not occur**. However, the platelets are consumed as these microthrombi form in every small blood vessel. Because red blood cells pass over these sharp little rocks, they experience **microangiopathic hemolytic anemia**—hemolysis, a low Hgb, and **schistocytes** on smear. Simultaneous formation in multiple small vessels

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compromises the delivery of blood to the distal tissues. TTP classically affects the brain and the kidneys. The mnemonic for TTP is FAT RN, and while it has nothing to do with the size of the nurse, stands for **f**ever, micro**A**ngiopathic anemia, **t**hrombocytopenia, **r**enal failure, and **n**eurologic dysfunction.

Only 5% of patients with TTP present with the pentad "FAT RN." The presence of microangiopathic hemolytic anemia (aka schistocytes) and thrombocytopenia alone should prompt consideration for TTP.

TTP	**Syndrome**	HUS
Adult	**Substrate**	Child
FAT RN	**Presentation**	Bloody diarrhea then renal failure
Acquired autoantibody to ADAMTS13	**Risk Factor**	Ate beef (EHEC O157:H7) or Epidemic dysentery at daycare (Shigella)
Plasma exchange	**Treatment**	Supportive care
Low	**ADAMTS13**	Normal

Table 4.1: TTP vs. HUS

You will not be asked to compare TTP to HUS. Consider them the same disease. What you will be asked to compare is TTP to DIC. In both cases there is platelet consumption and microangiopathic hemolytic anemia. In both, the CBC will show a low hemoglobin and low platelets. In both, there will be schistocytes on blood smear. The consideration of DIC and TTP will be made concurrently. The patient with TTP did not start off sick, but has rapidly gone in that direction with altered mental status and renal failure, whereas the patient with DIC started sick and developed bleeding and a deleterious change in the labs.

The clinical scenario can be augmented with DIC labs. In disseminated intravascular coagulation, fibrin thrombi form everywhere they shouldn't, consuming and depleting platelets and factors in the very places they are needed. In TTP, the microthrombi are platelet-only, so clotting factors are not consumed. That means, in TTP, the **PT, PTT, and INR are normal**, the **fibrinogen is normal**, and the **split products are not elevated**. We go into detail on this interpretation in the next section on DIC.

At the heart of TTP pathogenesis is a **deficiency of ADAMTS13**. The most common cause of TTP is an autoantibody (**acquired TTP**) against ADAMTS13. Less commonly, patients inherit an inactivating mutation that only sporadically causes disease and doesn't start until adolescence, implying that more than just the mutation leads to disease. You should learn that TTP is antibody mediated. Diagnosis is made by demonstrating **low ADAMTS13** and **ADMTS13 antibodies**. ADAMTS13 is a metalloproteinase that chops up von Willebrand multimers. With depressed ADAMTS13 function, von Willebrand multimers accumulate. These large protein macromolecules can activate platelets. Activation of platelets leads to aggregation, and the formation of those jagged rocks mentioned above. Patients with TTP require **plasma exchange** (PEX), the removal of plasma with antibodies and von Willebrand multimers, and the transfusion of plasma without them. This is NOT like plasmapheresis (which removes antibodies) or IVIG (which blocks antibody activity) used in ITP. PEX is required to remove the multimers.

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At the time that decision is made, ADAMTS13 levels cannot be reported (it is a send-out test). HUS is associated with normal ADAMTS13, and the pathogenesis of how Shiga toxin causes altered endothelial function is not well understood.

Never give platelets to TTP. The only result is more clot formation and more organ compromise. Plasma exchange is the only treatment. For those who cannot accept plasma exchange (Jehovah's Witnesses, for example), IVIG, corticosteroids, and plasmapheresis can be attempted.

Disseminated Intravascular Coagulation

While DIC and TTP share microangiopathic hemolysis and the formation of clots, they are completely distinct diseases. DIC causes both factor bleeding and platelet bleeding, demonstrating an elevation of the PT, PTT, and INR, as well as a thrombocytopenia. There are also venous clots. DIC can be in the acute, chronic, or subacute phases, which means, "*anyone can be in DIC with any labs.*" Thanks, science, for making things so clear. You should learn DIC as **only the acute disease**, the person who starts off with a severe, life-threatening illness, already ventilated and on vasopressors, who then starts bleeding from everywhere.

DIC is primarily induced by **abnormal initiation of clotting**. Two major mechanisms represent the trigger: release of tissue factor (thromboplastin) into circulation, and widespread endothelial injury.

Tissue factor is released by endothelial cells. It is also released from the placenta during obstetrical complications (a cause of DIC) and from tissues suffering burns or severe trauma (other causes of DIC). **Overwhelming** sepsis, with exposure of endotoxin-inducing release of widespread TNF-α, upregulates the expression of adhesion molecules on endothelial cells and downregulates thrombomodulin (anticoagulant), making it more likely for leukocytes to bind. Leukocytes release reactive oxygen species leading to endothelial damage.

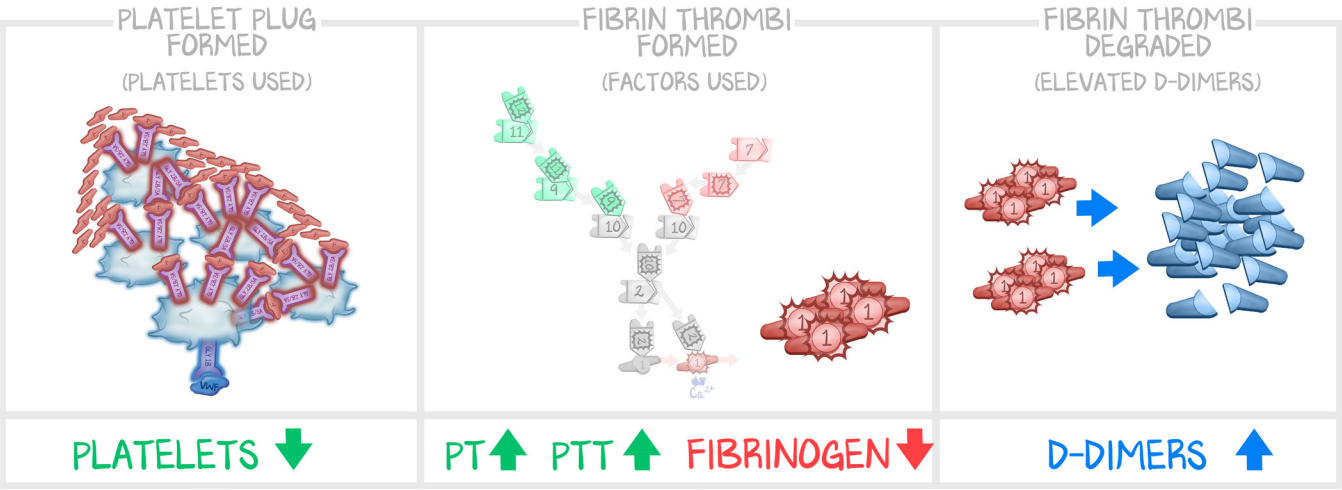

Figure 4.6: Disseminated Intravascular Coagulation (DIC) Labs
Platelets are used to make the platelet plug, and so excess consumption of platelets results in thrombocytopenia. Factors are used to make fibrin thrombi, and so factors so excess consumption results in a low fibrinogen (low factor 1). If the other factors' levels were measured they would be low. But that's not how we measure secondary hemostasis. Instead, we measure the PT and PTT, which will be elevated with decreased factors. Because more fibrin polymers are made, more plasmin degrades more polymers to split products, which are measured as an increased in D-dimer.

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Endothelial damage from any source results in the **release of thromboplastin** and the **exposure of subendothelial collagen**, which tip the system in favor of clotting. If this were happening in just one place, there would be no need for concern. But when it happens **everywhere at once**, many thousands of clots form, simultaneously consuming all the circulating resources needed for clotting. The normal mechanisms are still in play—platelets adhere, activate, and aggregate. Factors are activated and form fibrin thrombi. Plasmin degrades fibrin to split products. It's just that it happens so many times in so many places that **all of the clotting resources are consumed**.

The treatment for DIC is to reverse the underlying cause and support the patient through the crisis. **Cryoprecipitate** is used to replete fibrinogen, **PRBC** to replete the hemoglobin, **platelets** to replete platelets, and **FFP** to replete the factors. Prognosis is grim if the reversible cause isn't easily reversed (delivery of the fetus can end the DIC; ongoing antibiotics at day 16 on four pressors is likely to die rather than have their cause reversed).

The presentation of acute DIC is catastrophic. The leading presentation is **bleeding**. Patients bleed from IV sites, indwelling catheter sites, from their gums and mucosal surfaces. Hemorrhage is not arterial spray, as with a transected vessel, but from oozing and weeping venous bleeding that cannot be stopped. Their blood smear will show evidence of microangiopathic hemolytic anemia, caused by the red blood cells forced through small blood vessels with fibrin clots, shearing and destroying RBCs, as evidenced by **schistocytes**. Their **platelets are low**, as they were consumed to make diffuse platelet plugs. Unlike TTP, which did not form fibrin clots, DIC shows consumption of factors as evidenced by **an elevated PT, PTT, and INR**, and a **decreased fibrinogen**, the substrate that is used to make the fibrin monomers. Fibrin monomers form fibrin thrombi, which are degraded to split products by plasmin. With so many fibrin clots formed and subsequently degraded, **D-dimer is elevated**.

Thrombocytopenia Not Bleeding = HIT

Heparin-induced thrombocytopenia is a complication of heparin administration. Unless there is a history of HIT, where memory cells remained primed to identify heparin as an antigen, there needs to be a prolonged exposure to heparin to develop **HIT antibodies** (7–14 days of heparin administration). HIT antibodies are **IgG** against **platelet factor 4–heparin complexes**. Platelet factor 4 (PF4) is one of the substances found in α-granules. Binding of these antibodies **activates thrombosis** even while **destroying platelets**. Therefore, the patient presents with **thrombosis** (usually venous) and **thrombocytopenia**. Heparin must be discontinued, and another anticoagulant started to treat the thrombi. Non-heparin products such as **argatroban** (the direct thrombin inhibitor) can be used to bridge the patient to warfarin. The larger the heparin, the worse the risk of HIT.

In HIT, there is **no bleeding** and **no petechiae**; the platelets show a significant drop (> 50%) but generally stay above 20,000. The patient will have been exposed to heparin for 7–10 days, had a significant drop in platelets, and developed a new thrombosis. Heparin must therefore always be avoided.

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